Elevation of Plasma Brain Natriuretic Peptide Is a Hallmark of Diastolic Heart Failure Independent of Ventricular Hypertrophy

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OBJECTIVES We tested a hypothesis that elevation of the plasma level of brain natriuretic peptide (BNP) is one of the characteristics of patients with diastolic heart failure (DHF) independent of left ventricular (LV) hypertrophy.

BACKGROUND The clinical characteristics of DHF are not well acknowledged, although DHF has become a great social burden. Such a lack of clinical information leads to inaccuracy in the diagnosis of DHF. We have demonstrated enhancement of ventricular production of BNP with progression of maladaptive ventricular hypertrophy, but not with development of compensatory hypertrophy in an animal DHF model.

METHODS Of 372 patients who presented to the emergency department because of acute pulmonary congestion without acute coronary syndrome between January 1996 and May 2002, those with an ejection fraction ≥45% upon admission, who were stably controlled at least for a year in our outpatient clinics, comprised the DHF group (n = 19). A control group consisted of 22 hypertensive patients with a LV mass index greater than or equal to its minimum value of the DHF group and an ejection fraction ≥45%, in whom cardiac symptoms had not occurred. An elevation of BNP may be a hallmark of patients with or at risk of DHF among subjects with preserved systolic function independent of LV hypertrophy. (J Am Coll Cardiol 2004; 43:55–60) © 2004 by the American College of Cardiology Foundation

RESULTS Despite a similar distribution of LV mass index, the BNP level was higher in the DHF group than in the control group (149 ± 38 vs. 31 ± 5 pg/ml, p < 0.01). There was no difference in LV cavity size or parameters derived from pulsed Doppler transmitral flow velocity curves.

CONCLUSIONS An elevation of BNP may be a hallmark of patients with or at risk of DHF among subjects with preserved systolic function independent of LV hypertrophy. (J Am Coll Cardiol 2004; 43:55–60) © 2004 by the American College of Cardiology Foundation

The clinical syndrome of congestive heart failure (HF) occurs over a broad range of underlying left ventricular (LV) systolic function (1–4). Heart failure with normal or minimally impaired systolic function is attributed to diastolic dysfunction and is termed “diastolic heart failure” (DHF). It frequently occurs in the community, particularly in the elderly population, and leads to a poor prognosis (1,2,5–7). Thus, the economic impact of DHF is substantial (8,9), and there is a growing interest in this type of HF. Noninvasive methods, including Doppler echocardiography, cannot provide unequivocal evidence of LV diastolic dysfunction (10,11), and DHF has not yet been well characterized. These account for an absence of practical and definitive diagnostic criteria for DHF. Currently, the diagnosis of DHF is made primarily on the basis of symptoms and exclusion criteria (12). However, symptoms such as exertional dyspnea, paroxysmal nocturnal dyspnea, and pedal edema are not specific to HF. Some may well argue against the diagnostic criteria (13). The doubt about the diagnosis has limited the recognition of the clinical and social importance of DHF.

Hypertensive heart disease is a major underlying cardiovascular disease in DHF (1,2), and LV hypertrophy is likely related to DHF (14). However, a population-based cohort survey demonstrated that <20% of patients with LV hypertrophy progress to HF (4). Experimental and clinical studies suggest that LV hypertrophy can be divided into at least two types—adaptive and maladaptive hypertrophy—the latter being closely related to HF (15–17). Currently, maladaptive hypertrophy cannot be detected in clinical settings.

Brain natriuretic peptide (BNP) is a cardiac neurohormone specifically secreted from the ventricles (18). Elevation of the plasma BNP level is considered to reflect ventricular structural and functional alterations. Although its clinical utility as a biochemical marker of LV systolic dysfunction has been reported (19–21), its positive predictive value was only 10% to 20%. Previous in vitro studies showed a close relationship between BNP production and
myocyte hypertrophy (22,23). Of interest is that adaptive hypertrophy did not promote ventricular BNP production in Dahl salt-sensitive rats, and the promotion was provided only in the presence of maladaptive LV hypertrophy with fibrosis that led to symptomatic overt DHF (24). We tested a hypothesis that elevation of plasma BNP is one of the characteristics of patients with or at risk of DHF among subjects with preserved LV systolic function.

METHODS

Selection of patients. To enroll patients with a history of definitive overt DHF (DHF group) from the institutional medical records, we identified patients who presented to our hospital’s emergency department with definitive pulmonary edema with preserved systolic function between January 1996 and May 2002. During this period, 372 patients had an acute onset of dyspnea, respiratory distress, and pulmonary rales due to pulmonary congestion, as confirmed by chest radiography, in the absence of an acute coronary syndrome. Of these patients, those who met the following entry criteria were identified: 1) echocardiographic confirmation of ejection fraction (EF) ≥45% on admission; and 2) release of symptoms by treatment with diuretics and/or vasodilators after the emergent admission. Patients with congenital heart disease, severe valve disease, or renal failure (serum creatinine concentration >2.0 mg/dl) were excluded. The plasma BNP level temporarily increases with worsening of HF and gradually decreases after relief of symptoms. To exclude the effects of such fluctuational changes in plasma BNP level in association with acute worsening of HF, patients who were hospitalized within a year before the study enrollment were also excluded. Among the patients who met these criteria, the DHF group in this study comprised 16 patients who were hospitalized between January 1996 and January 2001 and agreed to participate in this study in January 2002, as well as three patients who were hospitalized between February 2001 and May 2002 and agreed to participate in May 2003. All of these patients were stable when they participated in this study. Two patients in the DHF group (11%) had a history of coronary artery disease. They had undergone a successful percutaneous coronary intervention before the episode of acute pulmonary congestion. At and after the emergent admission, there was no significant change in their electrocardiogram and no increase in plasma levels of troponin T and the MB isoenzyme of creatine kinase. They underwent coronary angiography after the release of the symptoms, and no significant coronary stenosis was found.

As a control group, 22 consecutive hypertensive patients referred for echocardiography who met all of the following criteria were included: 1) no symptoms of HF up to the study enrollment; 2) EF ≥45%; 3) a ratio of LV mass to body surface area (LV mass index) greater than or equal to the minimum value of LV mass index in the DHF group; and 4) >50 years old, because all the patients of the DHF group were >50 years old. These criteria were used because EF, LV mass index, and age are likely to individually affect the plasma BNP level (19–21,25), and their differences between groups will make it difficult to assess a relationship between plasma BNP level and DHF. Patients with severe valve disease or renal failure (serum creatinine concentration >2.0 mg/dl) were excluded. This study was approved by the institutional ethics committee, and all participants gave written, informed consent.

Study protocol. In the both groups, conventional transthoracic echocardiography and blood assay were conducted. Medications were not withheld before this study for ethical reasons.

Transthoracic echocardiographic examinations were conducted to measure left atrial and LV cavity sizes and LV wall thickness, as previously described (20,26,27). Ejection fraction was calculated by a modification of the method of Quinones et al. (28), and LV mass was calculated according to the formula derived from the data of the American Society of Echocardiography (29), as previously described (20,27). In patients with sinus rhythm, the pulsed Doppler transmirtal flow velocity curve was recorded to measure a ratio of peak mitral E-wave velocity to peak mitral A-wave velocity (E/A ratio) and the deceleration time of the mitral E-wave velocity (27).

Phlebotomy was performed to measure plasma concentration of neurohormones. Plasma concentrations of atrial natriuretic peptide (ANP) and BNP were measured using immunoradiometric assay with commercially available kits (Shionogi Co. Ltd., Osaka, Japan). Plasma renin activity and aldosterone level were measured using radioimmunoassay with commercially available kits (Dainabot Co. Ltd., Tokyo, Japan). The plasma norepinephrine concentration was measured by high-performance liquid chromatography.

Statistical analysis. Values are expressed as mean ± SEM. All statistical analyses were performed using a commercially available statistical software (STATVIEW version 5.0, SAS Institute Inc., Cary, North Carolina). Discrete variables were summarized by frequency percentages and analyzed with the chi-square test. Differences between the two groups were assessed using the Student t test. Results were considered statistically significant at p < 0.05.
Table 1. Patient Characteristics of Both Groups

<table>
<thead>
<tr>
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<th>Control Group</th>
<th>DHF Group</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>66 ± 2</td>
<td>72 ± 3</td>
</tr>
<tr>
<td>Women (%)</td>
<td>59</td>
<td>68</td>
</tr>
<tr>
<td>Medications (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>45</td>
<td>53</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>68</td>
<td>63</td>
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<tr>
<td>Diuretics</td>
<td>18</td>
<td>79*</td>
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<tr>
<td>Beta-blockers</td>
<td>23</td>
<td>37</td>
</tr>
<tr>
<td>Other vasodilators</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>Clinical history (%)</td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Coronary artery disease</td>
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<td>11</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<td>11</td>
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<tr>
<td>Atrial fibrillation (%)</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>133 ± 4</td>
<td>132 ± 4</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>77 ± 2</td>
<td>72 ± 2</td>
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<tr>
<td>Left ventricular end-diastolic dimension (mm)</td>
<td>50 ± 1</td>
<td>49 ± 2</td>
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<tr>
<td>Left ventricular end-systolic dimension (mm)</td>
<td>32 ± 1</td>
<td>31 ± 1</td>
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<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>68 ± 2</td>
<td>63 ± 2</td>
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<td>Interventricular septal thickness (mm)</td>
<td>12 ± 1</td>
<td>12 ± 1</td>
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<tr>
<td>Left ventricular posterior wall thickness (mm)</td>
<td>11 ± 1</td>
<td>11 ± 1</td>
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<tr>
<td>E/A ratio</td>
<td>0.79 ± 0.06</td>
<td>0.80 ± 0.06</td>
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<tr>
<td>Deceleration time of mitral E-wave velocity (ms)</td>
<td>196 ± 7</td>
<td>218 ± 16</td>
</tr>
<tr>
<td>Left atrial dimension (mm)</td>
<td>38 ± 1</td>
<td>44 ± 2*</td>
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<tr>
<td>Serum creatinine level (mg/dl)</td>
<td>0.8 ± 0.1</td>
<td>1.0 ± 0.1</td>
</tr>
</tbody>
</table>

*p < 0.05 versus control group. Data are presented as the mean ± SEM.

ACE = angiotensin-converting enzyme; DHF = diastolic heart failure; E/A = ratio of peak mitral E-wave velocity to peak mitral A-wave velocity.

RESULTS

Patient characteristics of the DHF and control groups at the time of the study enrollment are summarized in Table 1. There were no significant differences in age or gender between the two groups. All of the patients in the both groups had a history of hypertension, and there was no difference in systolic and diastolic blood pressures in the outpatient clinics.

The LV end-diastolic and end-systolic dimensions, EF, and wall thicknesses of the interventricular septum and LV posterior wall were not different between the groups. The LV mass index was similarly distributed between the groups (Fig. 1). The E/A ratio and deceleration time of the mitral E-wave velocity were not different. The left atrial dimension was significantly larger in the DHF group than in the control group.

Plasma BNP and ANP levels were significantly higher in the DHF group than in the control group (Fig. 1). There was no difference in the plasma levels of norepinephrine, renin activity, or aldosterone (Fig. 2).

At the time of study enrollment, 12 patients in the DHF group were in New York Heart Association (NYHA) functional class I; 5 patients were in class II; and 2 patients were in class III. The BNP level was significantly higher in the 12 patients of the DHF group with NYHA class I than in the control group (96 ± 29 vs. 31 ± 5 pg/ml, p < 0.01). In contrast, the statistical significance disappeared when the ANP level (52 ± 14 vs. 31 ± 3 pg/ml, p = 0.08) or left atrial dimension (40 ± 2 vs. 38 ± 1 mm, p = 0.23) was compared between the 12 DHF patients with NYHA class I and the control group.

DISCUSSION

Diastolic HF occurs in a high proportion of patients with HF and causes significant mortality and morbidity (1,2,5,6). It accounts for more than 25% of the total HF cost (8,9), and its prevalence may further increase as the population becomes older. The mortality impact of DHF was greater than that of HF with reduced EF (i.e., systolic HF) among community-dwelling elderly persons (7). However, diagnostic criteria for DHF have not been defined. The current consensus is that the assessment of LV diastolic function with the analysis of transmitral flow velocity curves has many limitations (10–12), particularly in patients with preserved EF (27,30). In fact, the diagnostic criteria for

Figure 1. Comparison of the left ventricular (LV) mass index, plasma brain natriuretic peptide (BNP) level, and plasma atrial natriuretic peptide (ANP) level between the two groups. The vertical bars indicate the range of values. The middle horizontal bars indicate means, and the upper and lower horizontal bars indicate standard errors (SEM).

Figure 2. Comparison of plasma norepinephrine level, plasma renin activity, and plasma aldosterone level between the two groups. The vertical bars indicate the range of values. The middle horizontal bars indicate means, and the upper and lower horizontal bars indicate standard errors (SEM). DHF = diastolic heart failure.
diastolic dysfunction, as proposed in several previous studies, are not consistent (14,31–33). The diagnosis based on symptoms of HF despite preserved EF is widely used but is argued against because the symptoms are not specific to HF (13). Thus, objective information on clinical characteristics of DHF is required to provide a reliable diagnosis.

To minimize the effects of such inconsistency in the diagnosis in the current study, the DHF group in this study consisted of patients who met the following criteria: 1) a history of acute onset of dyspnea, respiratory distress, and pulmonary rales due to pulmonary congestion, as confirmed by chest radiography; and 2) echocardiographic confirmation of preserved EF on admission. The current results show that the LV chamber dimension, LV mass index, and parameters derived from the transmitral flow velocity curves in the DHF group were not different from those in the control group consisting of hypertensive patients who had been asymptomatic. In contrast, the plasma BNP level was significantly higher in the DHF group than in the control group. Elevation of the plasma BNP level in symptomatic DHF patients was reported (3,34), but the DHF patients in these studies had LV hypertrophy. Previous in vitro and in vivo studies showed a close relationship between BNP production and myocyte hypertrophy (20,22,23); thus, it was unclear in their study whether the increased BNP level was due to LV hypertrophy or characteristic of DHF independent of LV hypertrophy. As LV hypertrophy is frequently associated with DHF (1,2,14), it is a clinically important issue whether BNP is increased in DHF patients beyond the level that is produced by LV hypertrophy alone. The current study expanded the previous findings by demonstrating that elevation of plasma BNP is not attributed to LV hypertrophy alone. This result is partly compatible with a previous study by Lang et al. (35), who demonstrated an increase in plasma BNP level in symptomatic DHF patients with ischemic heart disease in the absence of LV hypertrophy. This study also showed that the plasma BNP level stayed elevated in the DHF group, even after symptoms of HF were controlled to NYHA class I. Thus, the elevation of plasma BNP is likely a hallmark of patients with or at risk of DHF among subjects with preserved EF.

Left ventricular hypertrophy may be classified into adaptive and maladaptive hypertrophy, and the pharmacologic suppression of maladaptive hypertrophy prevented the transition to overt DHF, despite the presence of adaptive hypertrophy (16,36). Our experimental studies suggest that adaptive hypertrophy was induced at least partly through activation of calcineurin (37), and that maladaptive hypertrophy was provided by activation of the renin–angiotensin and endothelin systems (16,36). Another experimental study showed development of adaptive LV hypertrophy in the presence of pressure overload in angiotensin II type 1-receptor knockout mice (38). Previous in vitro studies showed that BNP production is enhanced in myocytes by adding G-protein–coupled neurohormones such as angiotensin II, endothelin-1, and phenylephrine (22,39), and ventricular BNP production was promoted by maladaptive, not adaptive, LV hypertrophy in hypertensive rats (24). Maladaptive hypertrophy was associated with progressive LV fibrosis that leads to myocardial stiffening (40). Tamura et al. (41) showed that pressure overload induced more progressive ventricular fibrosis in mice genetically lacking in BNP, as compared with wild mice. These findings suggest a close relationship between BNP production and ventricular fibrosis. Clarkson et al. (34) reported beneficial effects of short-term administration of BNP in patients with symptomatic DHF patients. Thus, elevation of plasma BNP in the DHF group may indicate the presence of maladaptive hypertrophy and/or progressive ventricular fibrosis, both of which play crucial roles in the development of DHF, and the enhanced production of BNP may act as a protective mechanism in DHF patients.

In this study, the plasma ANP level was also higher in the DHF patients than in the asymptomatic hypertensive patients with a similar LV mass index. Left atrial dimension was significantly enlarged in the DHF group. Because plasma ANP is mainly secreted from the atria (18), left atrial overload due to LV diastolic dysfunction may have enlarged the left atrium to elevate the plasma ANP level. Thus, an elevated plasma ANP level and enlarged left atrial dimension are likely another characteristic of DHF among subjects with preserved EF. However, in contrast to BNP, increases in these parameters are not beyond the level expected by the effects of LV hypertrophy alone in asymptomatic patients. The norepinephrine level was not different between the DHF and control groups. Kitzman et al. (3) showed that the norepinephrine level was higher in DHF patients than in normal healthy controls. All of the DHF patients in their study were asymptomatic. In contrast, more than half of the patients in the DHF group were controlled to NYHA class I in this study, although all of the patients had a history of acute pulmonary congestion. Even in symptomatic patients, most were controlled to NYHA class II. Ross et al. (42) demonstrated a decrease in plasma norepinephine to a normal level in association with the improvement of congestive HF by medical therapy in patients with congenital heart disease. These may at least partly explain an absence of the difference in norepinephrine level between the DHF and control groups.

Study limitations. There are some limitations of this study. First, the number of study subjects is not large. The DHF group in this study included only patients who had a definitive history of acute pulmonary edema under echocardiographic confirmation of EF ≥45% on admission and were still followed up by our outpatient clinics. The plasma BNP level temporarily increases with worsening HF and gradually decreases after relief of symptoms. The effects of such fluctuations in BNP were avoided by selecting patients who experienced acute pulmonary congestion more than one year before the study enrollment. Such strict inclusion criteria are responsible for the small number of the subjects but have minimized the effects of inaccuracy in the diagnosis.
of DHF that have been frequently debated in the discussion of the reliability of the conclusions of DHF studies.

Second, it is unclear whether the current findings can be extrapolated to patients with mild symptoms due to diastolic dysfunction and without a history of acute pulmonary edema. However, the current results suggest that a future prospective study with a large number of subjects to analyze the utility of plasma BNP as a diagnostic or predictive tool for DHF is promising.

Third, there was no significant difference in the parameters derived from Doppler echocardiography, except for left atrial dimension, between the DHF and control groups in this study. Redfield et al. (43) recently demonstrated that diastolic dysfunction defined by combined analysis of pulsed Doppler transmitral and pulmonary venous flow velocity curves and tissue Doppler imaging of mitral annular motion represented a poor prognosis. Because pulmonary venous flow velocity curves and mitral annular motion were not analyzed in this study, the current study does not necessarily deny the value of the additional Doppler echocardiographic parameters in characterizing patients with DHF. The principal purpose of this study was to test a hypothesis that elevation of plasma BNP is characteristic of patients with or at risk of DHF among subjects with preserved LV systolic function, and the lack of the analysis of such additional Doppler echocardiographic parameters should not lessen the clinical implication of this study.

Conclusions. We found that the plasma BNP level was elevated in patients with a history of acute pulmonary edema due to DHF independent of LV hypertrophy. Their BNP levels were still high even after their symptoms were controlled to NYHA class I. Thus, the elevation of BNP may be a hallmark of patients with or at risk of DHF among subjects with preserved LV systolic function.

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